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The impact of hormonal contraceptives on blood pressure, urinary albumin excretion and glomerular filtration rate

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Aim
In short-term studies, hormonal contraceptives (HC) have been suggested to induce a rise in blood pressure (BP) and urinary albumin excretion (UAE), while the effect of HC in renal function (GFR) is still under debate. Data on long-term and withdrawal effects of HC use on these outcomes are, however, not available. We therefore studied whether the start and cessation of HC induce changes in BP, UAE and GFR.

Methods
We used data from the PREVEND Study, a prospective cohort of subjects aged 28–75 years. Eligible were women aged ≤45 years with complete clinical and pharmacy data on baseline and follow-up screening (4 years later). Multivariate regression analysis was used to estimate the effects of HC on BP, UAE and GFR in those who started (n = 73), stopped (n = 117) or continued (n = 183) with those who never used HC (n = 286) as the reference group.

Results
BP increased among starters and fell in stoppers. These changes compared with never-users were statistically significant, even after adjustment for relevant variables. UAE increased by 14.2% in starters (P = 0.074) and fell by 10.6% in stoppers (P = 0.021), while GFR fell by 6.3% in starters (P < 0.001) and did not change in stoppers. The effects of stopping HC on UAE and GFR were significantly different compared with changes among never-users, even after adjustment for other variables (P = 0.023 and 0.036, respectively).

Conclusions
The start of HC was independently associated with worsening of BP, UAE and GFR, while stopping HC use resulted in an improvement. These data suggest that long-term HC use (aged 28–45 years) may be deleterious from the cardiovascular and renal point of view, but stopping may result in correction of these effects.

Introduction

Hormonal contraceptives (HC) have been used for more than three decades. Much attention has been drawn to the thromboembolic and cardiovascular adverse events associated with these agents. It has been generally acknowledged since 1978 [1] that HC may increase

blood pressure (BP). However, the activation of the renin–angiotensisn system (RAS), recently suggested to play a role in this mechanism of HC in elevated BP, is still a matter of debate [2–5]. Although the association between the use of HC and BP elevation has been repeatedly demonstrated [5–7], few studies have shown the beneficial effect on BP of cessation of HC [8, 9].

Epidemiological and pathophysiological data on HC use and the renal outcome, e.g. albuminuria and renal function, are limited. Interestingly, some studies have recently described an association between the use of HC and albuminuria [3, 5, 10]. Higher levels of albuminuria are considered an early marker of vascular endothelial damage [11, 12] and are related to an increased risk of progressive renal failure and excess cardiovascular morbidity and mortality [12–17]. The mechanism of the effect of HC on urinary albumin excretion (UAE) is still unknown, although there are studies showing that it may be related to a systemic haemodynamic effect, i.e. an increase in BP [1, 9, 18] or a specific renal effect [4, 19].

There is currently no evidence to suggest that HC use predisposes women to renal disease. However, studies on the association between HC and renal outcome have so far been conducted in hypertensive [5] or diabetic populations [3]. In the general population data are scarce. Two studies have proposed that the use of HC may be associated with an increased risk of microalbuminuria, independent of BP [5, 10]. The subjects included in our previous cross-sectional study [10] have now been followed for more than 4 years. Participants have been screened for a second time and their drug use has been monitored. We now present a prospective, observational study, performed in this cohort of women, investigating whether the long-term use of HC has an effect on BP, albumin loss and glomerular filtration rate (GFR).

Methods

Study design and population

This study is part of the PREVEND (Prevention of REnal and Vascular ENd-stage Disease) study, an ongoing, prospective study designed to investigate the impact of UAE on renal and cardiovascular disease progression in the general population. The formation of this cohort study has been previously described in detail [10, 20]. Briefly, in 1997 a cohort of subjects aged 28–75 years enriched for an elevated UAE was drawn from the population of the city of Groningen. Overall 8592 subjects gave written informed consent and were included in 1997 in the observational cohort for extensive baseline screening (baseline screening). The 8592 subjects, of whom 95% were caucasians, were followed up for cardiovascular and renal morbidity and mortality details since the time of their baseline screening. They were invited for a second screening after a mean follow-up period of 4.2 years (range 2.8–6.1). By then 246 subjects had died, 130 were lost to follow-up and 1322 declined participation, leaving 6894 subjects who completed the second screening. Of these 6894 subjects, only women were included ($n = 3450$). We excluded those aged >45 years ($n = 1880$) and those for whom no complete information on drug use during the follow-up period (4.2 years) was available ($n = 1129$). Thus, 751 subjects were available for further analysis. The changes in BP, UAE and GFR from baseline compared with the second screening were studied in relation to the use of HC.

Study measurements

The methodology used in the PREVEND cohort study has been described previously [10, 20]. The screening examinations included two visits to an outpatient clinic, the first visit including an interview on demographics, medical history and smoking habits. During a physical examination, weight, height and BP were measured. Body weight was measured to the nearest 0.5 kg, using a balance scale (seca Vogel & Halke GmbH & Co., Hamburg, Germany) after removal of shoes and heavy clothing. Height was measured to the nearest 0.5 cm using a statiometer measuring board with right angle. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). In the supine position, BP in the right arm was measured on two visits, every minute for 10 min using an automatic blood pressure monitoring device (Dinamap XL Model 9300; Johnson-Johnson Medical Inc., Tampa, FL, USA). Systolic BP (SBP) and diastolic BP (DBP) were calculated as the mean of the last two measurements at both visits. Fasting blood samples were drawn for direct measurement of total cholesterol, glucose and serum creatinine. Urine was also collected for 2 days for measurement of UAE.

Plasma glucose, serum cholesterol and serum and urinary creatinine were recorded based on the findings of an automated dry chemistry analyser system (Kodak Etachem; Eastmen Kodak, Rochester, NY, USA). Urinary albumin concentration was determined by nephelometry with a threshold of 1.8–2.3 mg l^{-1} and intra- and interassay coefficients of variation of <2.2% and <2.6%, respectively (Dade Behring Diagnostic, Marburg, Germany). UAE is given as the mean of the two 24-h urine excretions. GFR (ml min^{-1} 1.73^{-2}) was estimated using the Modification of Diet in Renal Disease (MDRD) formula: $186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$ [21].

Information on drug use

Information on drug use was obtained from the InterAction Database (IADB), containing pharmacy-dispensing data from community pharmacies in the city of Groningen. Dutch patients usually register at a single community pharmacy, which can therefore provide an almost complete listing of subjects' prescribed drugs [22]. Pharmacy data contain, among others, information on the name of the drug dispensed, Anatomical Therapeutical Chemical (ATC) classification, date of prescription and number of days the drug was prescribed and the number of defined daily doses (DDDs) based on the World Health Organization definition [23]. The use of over-the-counter (OTC) drugs and in-hospital prescriptions were not included. Information on drug use was collected from at least 1 year prior to the date of the first screening until at least the second screening.

Exposure definitions

HC were defined as preparations containing ethinyl estradiol and/or a progestin, either oral, injection or subcutaneus implant. The intrauterine device (IUD) and progestagen-only oral preparations (mini-pill contains low potency progesteron) are not considered HC in this study.

A subject was defined as using HC at the first screening if she had used at least one prescription of the drug in the year prior to the first screening. Women who had used HC at the first screening, but stopped its use more than 1 year before the second screening, were classified as 'stoppers' ($n = 117$) and those who continued to use it until the second screening [with a mean prescribed daily dose (PDD) during the observation period ≥0.75] were defined as 'continuers' ($n = 183$) (the PDD was calculated from the total amount of DDDs divided by the number of days of exposure). The women who did not use HC at the first screening but started to use it at least a year prior to the second screening were defined as 'starters' ($n = 73$). Women who had used the hormone for a short period in between the two screenings (intermediate use, $n = 92$) were not taken into account in this study. Women who had never used HC in the entire observation period were defined as 'non-users' ($n = 286$). We similarly recorded the use of antihypertensive medication, divided into agents interfering in the RAS, such as ACE inhibitors or angiotensin II receptor blockers, and other antihypertensives. The use of lipid-lowering and glucose-lowering drugs was also registered.

We also studied subgroups of oral HC users according to their progestin classified as second generation (levonorgestrel, lynestrel and norethindrone) or third generation (desogestrel, gestodene and norgestimate) [24]. Subjects who received HC of only one generation during the study period were included in the subgroup analyses for the type of generation of HC. Subjects who switched from one generation of HC to another were excluded from subgroup analysis for the type of HC generation.

Statistical analysis

Baseline characteristics are reported as mean and SD for continuous variables and as percentage for categorical variables. Because of its skewed distribution, logarithmic transformation of UAE was applied for further analyses and reported values are transformed back to the original scale (geometric means). Differences in population characteristics at baseline between the various groups under investigation were tested for continuous variables by Student's *t*-test for nonpaired data and for categorical variables by a χ^2 test.

We compared the percentage change in BP, UAE and GFR between the first and second screenings for each category of HC user with Student's *t*-test for paired data. One-way ANOVA was applied to test for changes in blood pressure, UAE and GFR between groups with never-users as reference. Multivariate linear regression models were built to adjust the baseline parameters that are known to influences changes in BP, UAE and GFR such as age, SBP and DBP, BMI, cholesterol, glucose, UAE and GFR. Similar analyses were performed to study the association between the various generations of HC and outcome. All calculations were performed with SPSS version 12.0.1 software (SPSS Inc., Chicago, IL, USA). A P-value <0.05 was considered to be statistically significant.

Results

Of the 751 women, 342 used HC at the time of the first screening, while 409 women did not. Among the 342 women who used HC at baseline, 117 (34.2%) stopped using the drug before the second screening (stoppers), whereas 183 (53.5%) were still using it at the time of the second screening (continuers) and 42 used HC <0.75 of DDD (intermediate). Of the 409 subjects who did not use HC at the baseline examination, 73 (17.8%) started use of HC before the second screening (starters), whereas 286 (69.9%) never used HC during the entire follow-up period (never-users) and 50 used HC only for a short period in between the two screenings (intermediate). Intermediate users ($n = 92$) were not included in further analysis.

The characteristics of these subjects at baseline according to their HC use at second screening are presented in Table 1. Women who never used HC were

Table 1
Baseline characteristics of the study cohort according to use of hormonal contraceptives (HC)

	Never-users $n = 286$	Starters $n = 73$	Continuers $n = 183$	Stoppers $n = 117$	*P*-value
Age (years)	39.1 (± 4.3)	37.4 (± 4.6)*	37.6 (± 4.6)*	36.5 (± 4.5)*	<0.001
Body mass index (kg m^{-2})	25.0 (± 4.4)	24.3 (± 3.6)	24.7 (± 3.8)	24.2 (± 4.3)	0.34
Systolic blood pressure (mmHg)	114.0 (± 13.3)	114.8 (± 10.5)	117.7 (± 13.3)*	114.6 (± 12.7)	0.02
Diastolic blood pressure (mmHg)	67.4 (± 8.0)	67.8 (± 7.5)	69.1 (± 7.7)	68.1 (± 7.4)	0.17
Glucose (mmol l^{-1})	4.4 (± 1.0)	4.4 (± 0.6)	4.3 (± 0.7)	4.4 (± 0.6)	0.71
Cholesterol (mmol l^{-1})	5.1 (± 1.3)	5.0 (± 1.0)	5.0 (± 1.5)	5.0 (± 0.9)	0.88
Urinary albumin excretion (mg 24 h^{-1})	8.4 (3.9, 18.4)	8.3 (4.4, 15.4)	9.7 (4.1, 23.0)	8.9 (4.5, 17.9)	0.23
Estimated glomerular filtration rate (ml min^{-1} 1.73 m^{-2})	82.1 (± 11.9)	81.1 (± 13.2)	78.3 (± 11.4)*	81.7 (± 10.0)	0.01
Smoking (%)	46.8	52.1	52.7	53.8	0.48
History of myocardial infarction (%)	0.7	0.0	0.5	0.0	0.74
Use of lipid-lowering drugs (%)	0.3	2.7	1.6	1.7	0.29
Use of statins (%)	0.0	2.7	1.6	1.7	0.11
Use of antihypertensives (%)	5.9	4.1	5.5	3.4	0.73
Use of renin – angiotensin system inhibitors (%)	1.4	0.0	1.1	1.7	0.74
Use of antidiabetics (%)	0.3	0.0	0.0	0.0	0.73

Continuous variables are presented as mean and SD; categorical variables are presented as percentage; urinary albumin excretion is presented as geometric mean and 95% confidence interval; P-*value indicates whether mean or prevalence of a certain variable differs between groups (using one-way* ANOVA *for mean and Pearson* χ^2 *for percentage).**P-*value < 0.05 indicates mean of a certain variable differs between this group compared with never-users using the Tukey test.*

older and had a lower SBP and higher GFR compared with those who used or had used HC. Other factors such as DBP, plasma cholesterol, glucose, smoking status, previous myocardial infarction, use of lipid- or BP-lowering drugs and antidiabetics were not significantly different between groups.

The effect of HC on SBP, DBP, UAE and GFR is shown in Table 2. The start of HC was associated with a rise in SBP and DBP, while SBP and DBP fell in stoppers. The percentage change in BP among starters and stoppers was statistically different from the change in the never-users for both SBP and DBP, also after adjustement for relevant variables.

A similar pattern is also found for UAE. Compared with the first screening, UAE at second screening increased by 14.2% ($P = 0.074$) in starters compared with 5.9% ($P = 0.081$) in those who never used HC, although the difference between these two groups did not reach statistical significance after adjustment for confounders ($P = 0.201$). In contrast, stopping HC use resulted in a decrease of 10.6% in UAE ($P = 0.021$). This decrease was significantly different compared with never-users, also after adjustment for others variables ($P = 0.023$).

GFR was lower at follow-up visit in starters ($P < 0.001$) and continuers ($P = 0.002$), but also fell in subjects who never used HC ($P < 0.001$), while GFR in stoppers did not change significantly. The fall in GFR was greatest in those who started HC compared with never-users and was smallest in those who stopped HC. The percentage reduction in GFR between stoppers *vs.* never-users was significantly different ($P = 0.036$) after adjustment for other variables.

When studying the second- and third-generation contraceptives separately (Table 3), starting a third-generation HC resulted in an increase in SBP and DBP compared with never-users. This was not the case among starters of a second-generation HC ($n = 45$). On the other hand, subjects who stopped a second-generation HC showed a lowering of SBP, while stoppers of a third-generation HC showed no difference in BP change compared with never-users. Starting use of either a second- or third-generation HC resulted in an increase in UAE, although these increases were not significant after adjustment compared with never-users. The rise in UAE was greatest among women who continued the use of a third-generation HC (+33.2%), whereas the fall in UAE was most pronounced among subjects who stopped a

Table 2
Use of hormonal contraceptives in relation to blood pressure urinary albumin excretion and glomerular filtration rate

Type of HC user	*N*	First screening	Second screening	*P*-value*	% change	*P*-value†
Systolic blood pressure (mmHg)						
Never-users	286	114.0 (±13.3)	113.9 (±12.7)	0.838	+0.3 (±8.5)	Reference
Starters	73	114.8 (±10.5)	117.7 (±12.3)	0.023	+2.8 (±9.1)	0.002
Continuers	183	117.7 (±13.3)	117.4 (±14.2)	0.664	−0.02 (±8.4)	0.162
Stoppers	117	114.6 (±12.7)	111.7 (±12.6)	0.001	−2.3 (±7.2)	0.041
Diastolic blood pressure (mmHg)						
Never-users	286	67.4 (±8.0)	68.1 (±7.6)	0.035	+1.4 (±8.0)	Reference
Starters	73	67.8 (±7.5)	70.0 (±7.1)	0.002	+3.6 (±8.5)	0.008
Continuers	183	69.1 (±7.7)	70.0 (±8.6)	0.041	+1.6 (±8.6)	0.152
Stoppers	117	68.1 (±7.4)	67.0 (±7.5)	0.020	−1.4 (±7.5)	0.015
Urinary albumin excretion (mg 24 h^{-1})						
Never-users	286	8.4 (3.9, 18.4)	8.9 (4.0, 20.0)	0.081	+5.9 (−0.7/12.8)	Reference
Starters	73	8.3 (4.4, 15.4)	9.5 (3.7, 23.9)	0.074	+14.2 (−1.0/31.9)	0.201
Continuers	183	9.7 (4.1, 23.0)	9.9 (4.1, 24.3)	0.580	+2.3 (−5.7/11.0)	0.809
Stoppers	117	8.9 (4.5, 17.9)	8.0 (4.3, 14.8)	0.021	−10.6 (−18.7/−1.8)	0.023
e-Glomerular filtration rate (ml min^{-1} 1.73 m^{-2})						
Never-users	286	82.1 (±11.9)	78.7 (±13.1)	<0.001	−4.0 (±10.7)	Reference
Starters	73	80.8 (±13.2)	75.0 (±13.2)	<0.001	−6.3 (±13.0)	0.074
Continuers	183	78.3 (±11.4)	76.2 (±13.2)	0.002	−2.4 (±10.9)	0.409
Stoppers	117	81.7 (±10.0)	80.5 (±11.0)	0.167	−1.0 (±11.3)	0.036

Urinary albumin excretion (UAE) is presented in geometric mean and 95% confidence interval; % change systolic (SBP) and diastolic blood pressure (DBP) and estimated (e-) glomerular filtration rate are presented as mean and SD; P-value indicates whether UAE, SBP, DBP and e-GFR differs between first and second screening (using paired sample t-test); P-value† associated with dummy variable for group, adjusted for baseline age, SBP, DBP, cholesterol, glucose, UAE and body mass index (using multivariate linear regression analysis); including the use of antihypertensives at baseline in the model did not change the result.*

second-generation HC (−16.9%) and both were significant compared with never-users after adjusting for confounding factors. The changes in GFR among starters, continuers or stoppers of HC, either a second or third generation, were not significantly different compared with never-users (Table 3).

Discussion

We found that the start of HC may induce a rise in SBP and DBP with an, albeit, insignificant rise in UAE and fall in GFR. Cessation of the use of HC was associated with a statistically significant fall in SBP, DBP and UAE, and a preservation of kidney function.

This study is the first to evaluate the effect of HC use on BP and renal outcome in the general population during long-term follow-up and also considers the effect of the withdrawal of HC. Short-term studies have showed that the administration of HC is associated with a rise in BP [5–7]. Ribstein *et al.* [5] reported that both in normotensive and hypertensive subjects, HC users had a significantly higher BP compared with non-users. Activation of the RAS is considered as an important factor leading to the increase in BP, since estradiol administration stimulates the hepatic synthesis of angiotensinogen [2, 25]. In another study, Lubianca *et al.* [8] have reported a significant decrease in SBP and DBP in women who stopped the use of contraceptives compared with those who did not. Thus, our long-term observational data on BP confirm the findings of short-term intervention studies.

Regarding the effects of HC on UAE, various short-term studies and cross-sectional epidemiological studies have shown an association of HC use and urinary albumin loss [3, 5, 10]. Our previous study, for example, using data of the first screening of the PREVEND cohort, showed that women receiving HC had a 90% increased risk for microalbuminuria (UAE 30–300 mg day^{-1}) compared with non-users [10]. Ribstein *et al.* [5] found a significant increase in 24-h UAE in normotensive as well as hypertensive women using oral contra-

Table 3
Change in blood pressure, urinary albumin excretion and glomerular filtration rate according to different generation of hormonal contraceptives

Type of HC user	Second generation of HC			Third generation of HC		
	N	% change SBP	*P*-value†	*N*	% change SBP	*P*-value†
Never-users	286	+0.3 (±8.5)	Reference	286	+0.3 (±8.4)	Reference
Starters	45	+0.4 (±7.3)	0.379	17	+5.3 (±12.0)	0.004
Continuers	100	−0.7 (±7.6)	0.519	30	+0.7 (±7.1)	0.733
Stoppers	67	−2.5 (±7.2)	0.045	26	−0.2 (±7.9)	0.896
	N	% change DBP	*P*-value†	*N*	% change DBP	*P*-value†
Never-users	286	+1.4 (±8.0)	Reference	286	+1.4 (±8.0)	Reference
Starters	45	+2.1 (±7.8)	0.282	17	+6.1 (±10.2)	0.010
Continuers	100	+1.3 (±8.6)	0.171	30	+0.5 (±6.6)	0.437
Stoppers	67	−1.2 (±7.7)	0.093	26	+0.2 (±7.7)	0.658
	N	% change UAE	*P*-value†	*N*	% change UAE	*P*-value†
Never-users	286	+5.9 (−0.7/12.8)	reference	286	+5.9 (−0.7/12.8)	Reference
Starters	45	+14.3 (−7.1/40.5)	0.188	17	+19.6 (−6.2/52.6)	0.465
Continuers	100	−5.6 (−15.1/4.9)	0.663	30	+33.2 (6.4/66.6)	0.032
Stoppers	67	−16.9 (−28.0/−4.2)	0.011	26	+7.5 (−7.0/24.3)	0.788
	N	% change e-GFR	*P*-value†	*N*	% change e-GFR	*P*-value†
Never-users	286	−4.0 (±10.7)	Reference	286	−4.0 (±10.7)	Reference
Starters	45	−6.7 (±13.9)	0.052	17	−9.2 (±9.2)	0.058
Continuers	100	−1.0 (±11.4)	0.057	30	−4.8 (±10.0)	0.422
Stoppers	67	−1.4 (±10.0)	0.183	26	−1.3 (±14.5)	0.195

HC (hormonal contraceptives); urinary albumin excretion (UAE; mg 24 h^{-1}) are presented in geometric mean and 95% confidence interval; % change systolic and diastolic blood pressure (SBP and DBP; mmHg) and estimated glomerular filtration rate (e-GFR; ml min^{-1} 1.73 m^{-2}) are presented in mean and SD. P-value† *associated with dummy variable for group, adjusted for baseline age, SBP, DBP, cholesterol, glucose, UAE, and body mass index (using multivariate linear regression analysis); including the use of antihypertensives at baseline in the model did not change the result.*

ceptives when compared with non-users. Similar results were observed in a recent study in a diabetic population by Ahmed *et al.* [3], who reported that in this population 18% of contraceptive users developed macroalbuminuria (UAE >300 mg day^{-1}) compared with 2% in non-users (relative risk =8.90). Interestingly, in our study a significant reduction in UAE was observed among women that stopped the use of HC, suggesting a reversible effect after discountinuation of HC. This fall in albuminuria was seen in stoppers of second-generation HC but not in those who stopped third-generation HC.

It is of interest that our study is able describe age-related changes in renal function over time. It is well known that renal function will decrease with age. We found that, compared with women who never used HC, those who started to use HC tended to have a greater decline in GFR over time, while those who stopped HC had less decline in GFR. At first sight this seems to conflict with data that showed that HC users have similar [5] or a higher [3] GFR than non-users. This led these authors to suggest that HC use may be associated with glomerular hyperfiltration, thus also explaining the risk of microalbuminuria. Our data suggest long-term use of HC induces a fall in GFR. However, the reassuring finding of our data is that these unfavourable effects of HC are reversible after withdrawal, even after many years.

We separately studied whether these renal effects of HC were seen more in second- *vs.* third-generation OC. Our data do not allow firm conclusions on this issue, partly because there were only few women on third-generation agents. If any conclusion can be drawn, there may be a tendency for stopping HC use to result in an improvement in BP, UAE and GFR in women using second-generation HC, while there were no changes observed in stoppers of third-generation HC. This suggests that third-generation HC may be more deleterious

than second-generation HC from a renal aspect. This may be in agreement with the data that there is a relationship between HC use and inflammatory markers, in particular in women taking third-generation agents. The latter has been argued to contribute to an increased risk of atherothrombotic [6] and peripheral arterial disease [26]. A recent prospective, cross-over, randomized study found no association between second- and third-generation HC and inflammation markers such as the concentration of serum C-reactive protein [27]. A recent meta-analysis by Baillargeon *et al.* [28] reported an increased risk of both cardiac and vascular events among second- and third-generation OC users; however, the risk in third-generation users seems less than in second-generation users.

Several potential limitations of the present study should be considered. First, we were able to analyse only half of the women who had participated in the previous screening, because approximately 20% of the women withdrew consent and from participating women only 60% had complete information on pharmacy data for the entire study period. However, the baseline characteristics of the women who were lost to follow-up did not differ statistically significantly from those who remained in the study, suggesting that loss to follow-up was not an important source of bias. Second, this study did not include women <28 years old and a high percentage of our population were current or past smokers at baseline. Third, bias may have been introduced through confounding by indication or contraindication for HC use. This may apply particularly to women on third-generation agents, since these preparations were originally introduced to protect against myocardial infarction due to their favourable effect on the lipid profile [29]. The major strength of this study is that we were able to provide long-term prospective follow-up with monitoring of pharmacy records in a large sample of the general population. Furthermore, its design enabled us to compare the effect of HC in women who used HC at first screening but stopped it afterwards, *vs.* subjects who never used these agents, used them continuously, or started their use.

In conclusion, the use of HC on women aged 28–45 years is independently associated with a worsening of BP, UAE and GFR, while stopping HC use resulted in an improvement. With respect to the generation of HC, our data suggest that third-generation might be more deleterious than second-generation HC. These data suggest that long-term use of HC may be deleterious from a cardiovascular and renal point of view, but stopping may result in reversal of these effects.

Conflict of interest

None declared.

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